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Palladium-Catalyzed Oxidative sp^2 C–H Bond Acylation with Aldehydes

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Abstract: An efficient method was developed for the direct acylation of arene sp^2 C–H bonds with aldehydes using palladium acetate as catalyst and peroxide as oxidant. The solvent-free oxidative acylation reaction assisted by a pyridine directing group provides an easy access to aromatic, aliphatic, and optical active ketones.

Keywords: acylation; aliphatic aldehydes; C–H functionalization; oxidative cross-coupling; palladium catalysis

Metal-catalyzed direct selective functionalization (of an arene) by unactivated C–H bond cleavage has attracted considerable attention because it is ecologically and economically advantageous compared to traditional cross-coupling methods employing organometallic reagents.[1] Nevertheless, in most cases these reactions still require a functionalized partner to generate the desired C–C bond [Figure 1, Eq. (1)]. The C–H bond adjacent to a heteroatom or a double bond can be selectively functionalized; we and others have developed various methods to generate C–C bonds directly from two different C–H bonds in the presence of an oxidizing reagent through a cross-dehydrogenative coupling (CDC) catalyzed by copper, iron or other transition metals [Figure 1, Eq. (2)].[2]

$$C^1\text{-}H + FG\text{-}C^2 \xrightarrow{\text{cat. M}} C^1\text{-}C^2 \quad (1)$$

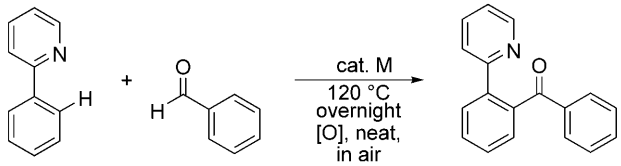
FG = Functional group

$$C^1\text{-}H + H\text{-}C^2 \xrightarrow[[O]]{\text{cat. M}} C^1\text{-}C^2 \quad (2)$$

Figure 1. Metal-catalyzed C–H bond functionalization and CDC reactions.

In recent years, the coupling of two aryl C–H bonds for the synthesis of an arene-arene linkage has witnessed remarkable progress.[3] In a challenging fashion, we recently reported the direct cross-coupling of an unactivated arene C–H bond with a cyclic alkane to produce a new Csp^3–Csp^2 bond.[4] On the other hand, there are reported methods for the carbonylation of arene compounds but they are often limited by the prefunctionalization of the substrates or by the necessity to handle toxic carbon monoxide gas.[5] In order to overcome these limitations, we postulated the C–C bond formation *via* cross-dehydrogenative-coupling between aromatic C–H bonds and aldehydes (Table 1).

Table 1. Optimization of the reaction conditions.



1a (0.2 mmol) **2a** (0.4 mmol) **3a**

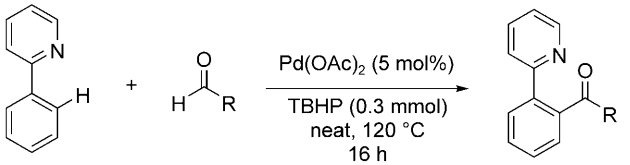
Entry	Catalyst (mol%)	Oxidant [O]	Yield [%][a]
1	$[RuCl_2(p\text{-cymene})]_2$ (5)	$(t\text{-BuO})_2$	ND[b]
2	Ru_3CO_{12} (5)	$(t\text{-BuO})_2$	ND
3	Rh(COD)Cl (2)	$(t\text{-BuO})_2$	ND
4	$PdCl_2$ (5)	$(t\text{-BuO})_2$	50
5	$PdCl_2$ (5)	*t*-BuOOH	70
6	$PdCl_2$ (5)	O_2 (1 atm.)	< 5
7	$Pd(OAc)_2$ (5)	*t*-BuOOH	> 95
8	$Pd(OAc)_2$ (1)	*t*-BuOOH	40

[a] NMR yield using an internal standard based on starting material **1a**.
[b] Not determined.

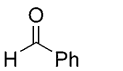
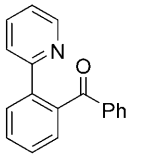
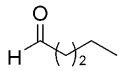
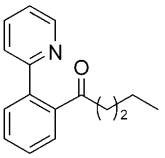
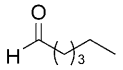
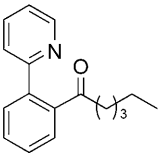
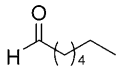
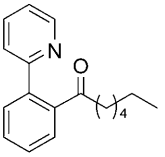
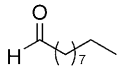
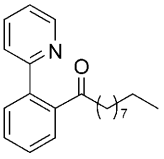
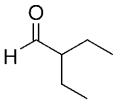
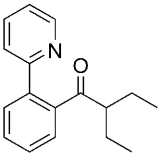
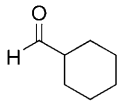
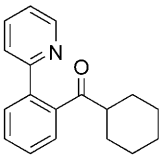
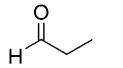
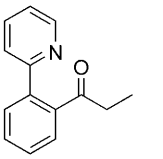
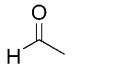
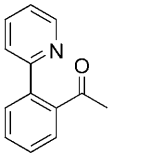
Our first attempt employing the previously reported ruthenium-catalyzed oxidative cross-coupling method[4] failed to generate the desired ketone coupling product of 2-phenylpyridine with benzaldehyde. Moreover, none of the tested ruthenium and rhodium[6] complexes have shown any catalytic activity under the described conditions. Many research groups have focused on exploring the Pd-catalyzed coupling reaction with C–H bonds through cyclopalladation assisted by directing groups.[1b,c] As a representative example, we recently developed an aromatic C–H bond methylation reaction with *tert*-butyl peroxide catalyzed by a palladium(II) salt.[7] In the present work, when palladium(II) chloride was employed as a catalyst together with *tert*-butyl peroxide (Table 1, entry 4), the expected acylated product was obtained in 50% yield with a similar conversion. Replacing the oxidant by *tert*-butyl hydroperoxide (TBHP) offered the ketone product in 70% yield as a single regioisomer (Table 1, entry 5). Oxygen, the ideal oxidant, was also tested under these conditions, but only a trace amount of the product could be detected by GC-MS (Table 1, entry 6). An excellent yield was achieved combining $Pd(OAc)_2$ as a catalyst and TBHP as an oxidant. During the course of our research, Cheng and co-workers reported a similar acylation reaction between arene C–H bonds and aromatic aldehydes catalyzed by $Pd(OAc)_2$ using xylenes as a solvent under an atmosphere of oxygen gas.[8] When replacing aromatic aldehydes by various aliphatic aldehydes, the desired acylation product was not obtained by Cheng and co-workers. Under the current solvent-free conditions, the scope of the palladium-catalyzed oxidative acylation reaction was also applicable to aliphatic aldehydes. Indeed, the method presented herein provides a solvent-free alternative to the previously reported method, and overcomes its major limitations.

Next, we examined the scope of the oxidative acylation reaction. Despite the use of benzaldehyde, which offered the desired ketone in very good yield, we concentrated our attention on *the unprecedented study of aliphatic aldehydes*. Simple aliphatic adehydes, such as decanal, heptanal, hexanal offered the desired coupling products in satisfactory yields when employed in a slight excess (Table 2, entries 3, 4, and 5). For lower boiling point aldehydes such as pentanal and propanal, a larger excess of the aldehyde had to be used in order to obtain the desired products in similar isolated yields (Table 2, entries 2 and 8). Under the optimized conditions, branched and cyclic aldehydes offered products **3f** and **3g** in good yields. An interesting feature of this new oxidative acylation procedure is the possibility to use acetaldehyde as a substrate to produce commercially important acetophenone derivatives. In regards of the low boiling point of this aliphatic aldehyde, the reaction was per-

Table 2. Scope of the oxidative acylation reaction.[a]



1 **2** **3**

Entry	Aldehyde (equiv.)	Product	Yield [%][b]
1	 **2a** (2)	 **3a**	83
2	 **2b** (4)	 **3b**	42
3	 **2c** (2)	 **3c**	51
4	 **2d** (2)	 **3d**	55
5	 **2e** (2)	 **3e**	51
6	 **2f** (3)	 **3f**	83
7	 **2g** (2)	 **3g**	81
8	 **2h** (5)	 **3h**	49
9	 **2i** (10)	 **3i**	71

[a] 2-Phenylpyridine **1** (0.2 mmol).
[b] Isolated yield based on pyridine substrate.

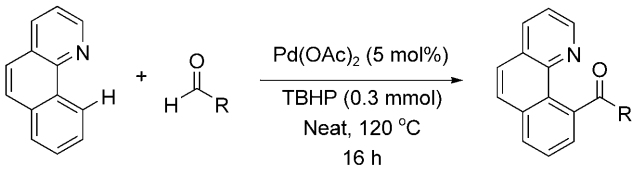
formed with a large excess of substrate **2i** to produce the acetophenone derivative product **3i** with a remarkably good yield.

Then we investigated the use of benzo[*h*]quinoline (**4**) as the arene substrate. The planar geometry of **4** is considered to be responsible for the high efficiency of the metal-catalyzed C–H bond functionalization generally observed.[9] In fact, good yields were obtained for all aliphatic aldehyde substrates. Acetaldehyde was also coupled with high efficiency under the described conditions. Nevertheless, the acetophenone derivative product (**5e**) was isolated along with a non-separable by-product. This by-product appeared to result from the aldol condensation of the ketone product with another equivalent of acetaldehyde. The identity the α,ß-unsaturated ketone (**5g**) was confirmed by reacting crotonaldehyde with benzo[*h*]quinoline under the optimized conditions (Table 3, entry 6).

The aldehyde functionality is abundant in nature. With this new methodology in hand, we considered the possibility to cross-couple optical pure natural products with arenes. Interestingly, citronellal[10] reacted in high efficiency with benzo[*h*]quinoline to produce the enantiomeric pure ketone **5h** without racemization (Scheme 1).

In order to acquire a better understanding of the reaction mechanism, the palladium dimer complex **A** was synthesized according to the literature procedure.[11] Considering **A** as a potential active species in the catalytic cycle, the reaction to produce ketone **5c** was tested in the presence of a catalytic amount of the palladacycle. The use of **A** as a catalyst offered the desired ketone product with the same yield as when $Pd(OAc)_2$ was employed. After formulating the hypothesis that the *in situ* formation of **A** constitutes the first step of the postulated catalytic cycle, we decided to investigate the reactivity of this particular palladium complex in the presence of aldehydes (Scheme 2). When **A** was stirred with the aliphatic aldehyde **2f** in the absence of peroxide and under an argon atmosphere, no desired product was detected. Importantly, under the same conditions, benzaldehyde appeared to be totally unreactive. In fact, all the non-oxidative conditions tested to demonstrate *path A* failed to produce the desired coupling product. These

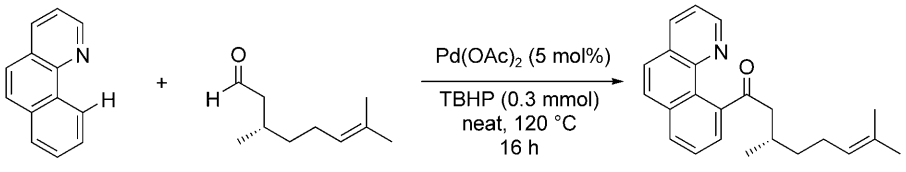
Table 3. Oxidative acylation of benzo[*h*]quinone.[a]



4 **2** **5**

Entry	Aldehyde (equiv.)	Product	Yield [%][b]
1	**2a** (2)	**5a**	85
2	**2e** (2)	**5b**	72
3	**2f** (3)	**5c**	89
4	**2g** (2)	**5d**	78
5	**2i** (10)	**5e+5g** 80:20	
6	**2j** (3)	**5j**	29

[a] Benzo[*h*]quinoline **4** (0.2 mmol).
[b] Isolated yield based on pyridine substrate.

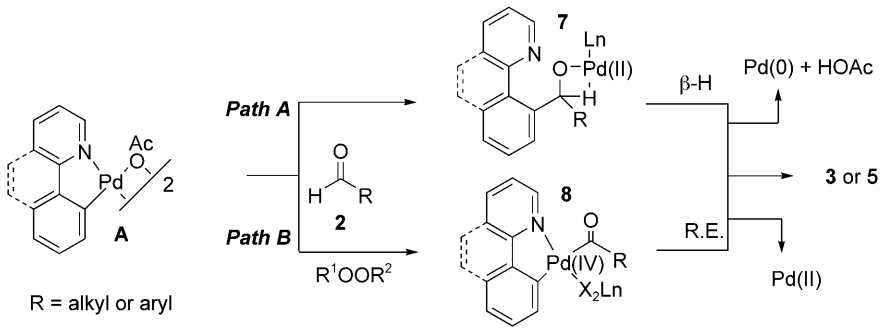


0.2 mmol

0.4 mmol
(*S*)-(–)-Citronellal (**2k**)

isolated yield: 61%
5h

Scheme 1. Oxidative acylation with enantiomeric pure citronellal.



Scheme 2. Possible mechanisms for the oxidative acylation.

results tend to demonstrate that a catalytic cycle involving Pd(II)/Pd(0) is unlikely to be operative. Palladium(IV) complexes have been proposed as key intermediates in the oxidative direct C–H bond functionalization of arenes and the Stanford group has recently clearly demonstrated the dramatic role of these high oxidation state palladium species.[12] Therefore, *path B* should be considered as a reasonable alternative. The oxidation of the Pd(II) complex (**A**) by peroxide in the presence of an aldehyde would generate a Pd(IV) intermediate (**8**). Intermediate **8** would undergo reductive elimination to produce the desired acylated product and re-generate Pd(II).

In summary, we have developed a highly efficient Pd-catalyzed pyridine-directed oxidative sp^2 C–H bond acylation with aldehydes. This new methodology enabled cross-coupling with both aromatic and aliphatic aldehydes in high yield and high regioselectivity. Investigations into the Pd(II)/(IV) catalytic cycle along with characterization of postulated intermediates and extension of the scope are ongoing and will be reported in due course.

Experimental Section

Typical Procedure for sp^2 C–H Bond Acylation

$Pd(OAc)_2$ (2.3 mg, 0.01 mmol), 2-phenylpyridine (29 μL, 0.2 mmol), and cyclohexanecarboxaldehyde (49 μL, 0.4 mmol) were placed inside a 10-mL glass vial. The vial equipped with a cap (Teflon septum inside) was sealed and immersed in an oil bath at 120 °C. TBHP (5 M in decane; 60 μL, 0.3 mmol) was added dropwise with a syringe through the septum and the reaction mixture was kept under stirring for 16 h. The resulting mixture was extracted with ethyl acetate and filtered through a short layer of silica gel eluting with ethyl acetate. The solvent was evaporated and the residue was purified by column chromatography on silica gel (eluent: hexane/ethylacetate = 2:3) to give the desired product **3g**; yield: 43 mg. ^{1}H NMR (500 MHz, $CDCl_3$, 293 K): $\delta = 8.65$ (d, 1H, $J = 4.5$ Hz), 7.76 (dt, 1H, $J_1 = 2$ Hz, $J_2 = 8$ Hz), 7.63 (d, 1H, $J = 8.5$ Hz), 7.59 (d, 1H, $J = 8$ Hz), 7.49 (dt, 1H, $J_1 = 7.5$ Hz, $J_2 = 1.5$ Hz), 7.41–7.45 (m, 2H), 7.23–7.25 (m, 1H), 2.22 (tt, 1H, $J_1 = 3$ Hz, $J_2 = 11.5$ Hz), 1.64–1.73 (m, 4H), 1.53–1.55 (m, 1H), 1.36 (qd, 2H, $J_1 = 3$ Hz, $J_2 = 12.5$ Hz), 1.08–1.15 (m, 1H), 0.96–1.02 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$, 293 K): $\delta = 209.4$, 157.9, 149.4, 141.3, 138.9, 136.9, 130.0, 129.4, 128.5, 128.3, 122.9, 122.1, 53.1, 22.9, 11.2; IR: $\nu_{max} = 2961$, 2930, 2873, 1684, 1586, 1460, 1438, 1426, 748, 729 cm^{-1}; HR-MS: $m/z = 266.1538$, calculated for $C_{18}H_{20}ON$ (M+1): 266.1539.

Acknowledgements

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